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Beclomethasone dipropionate 250 μg per dose metered dose inhalers: effect of Volumatic spacer on potentially respirable dose

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Abstract

The aerodynamic particle size distribution of beclomethasone dipropionate from 250 μg per dose metered dose inhalers tested in conjunction with a Volumatic spacer, was studied using a multistage liquid impinger. The products tested were Becloforte (Allen and Hanburys), Becloforte (parallel import from Spain), Beclazone 250 (Norton Healthcare) and Filair Forte (3M Health Care). Tests were performed with either zero or 3 s time delay between actuation of the inhaler and sampling. Filair Forte gave significantly lower deposition than all the other products in both the <6.8 and <3.1 μm size ranges with both zero and 3 s residence times (49.8% less than Becloforte, UK-origin, at <6.8 μm, zero residence time). This was despite fitting well in the Volumatic. Testing a second batch of Filair Forte confirmed the low deposition results. The only other significant differences were greater depositions from Becloforte (Spanish) compared to Beclazone 250 (<6.8 μm, zero residence time and <3.1 μm, 3 s residence time) and between Becloforte (Spanish) and all the other products (<3.1 μm, zero residence time). The magnitude of these differences were, however, less marked than those shown by Filair Forte. Increasing the residence time of the aerosol in the Volumatic to 3 s, simulating how patients may use the inhaler/spacer combination, gave similar results to those obtained with zero residence time. Filair Forte, used with the Volumatic, delivered a relatively low dose in the potentially respirable size range, compared to Becloforte. No substantial differences were seen at <6.8 μm between Becloforte (UK or Spanish) or Beclazone 250. Further work would be required to determine the importance of the differences observed between the products in the <3.1 μm range. © 1997 Elsevier Science B.V.

Keywords: Aerodynamic particle size; Beclomethasone dipropionate; High performance multistage liquid impinger; Metered dose inhaler; Volumatic spacer

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1. Introduction

The aerodynamic size of drug particles emitted from a metered dose inhaler (MDI) is increased due to unevaporated propellant. This, together with the high velocity of the aerosol, contributes to oropharyngeal drug deposition. The use of an MDI with a spacer device reduces deposition in the oropharynx by slowing the particles, allowing time for propellant to evaporate and causing large particles to sediment (Gonda, 1992). In the case of inhaled steroids, this can reduce the incidence of adverse effects such as hoarseness and fungal infection. A large volume spacer also reduces the need for co-ordination between inspiration and actuation of the MDI (Keeley, 1992).

The amount of drug in the potentially respirable aerodynamic particle size range varies considerably for a particular MDI, depending on the spacer used (Kim et al., 1987; Hindle and Chrystyn, 1993; Holzner and Müller, 1994; Ahrens et al., 1995; Chege et al., 1995; Barry and O'Callaghan, 1995, 1996). Similar differences have been found in vivo, using an evaluation of total lung bioavailability (Hindle and Chrystyn, 1994). Also, the relative suitability of the spacer varies with the drug formulation used (Kim et al., 1987; Ahrens et al., 1995; Barry and O'Callaghan, 1996). It has been recommended that any particular MDI/spacer combination should be evaluated before being prescribed (Crompton and Prowse, 1994; Ahrens et al., 1995; Barry and O'Callaghan, 1996; Kmietowicz, 1996).

Relatively little has been published regarding the compatibility of generic inhalers with spacers, compared with the proprietary products. Chege and Chrystyn (1994), using an evaluation of total lung bioavailability, found a generic salbutamol inhaler to be equivalent to the proprietary MDI, when used with the Volumatic spacer. Holzner and Müller (1994) studied two sodium cromoglycate MDI formulations, finding that, with eight types of spacer, one of the formulations gave higher doses in the respirable size range than the other. With a ninth type of spacer, the other formulation was favoured.

Concern has been expressed (Crompton and Prowse, 1994) about the equivalence of generic beclomethasone dipropionate (BDP) MDI formulations with the original proprietary product, different strengths of which have the brand names Becotide/Becloforte, marketed in the UK by Allen and Hanburys. Laurikainen et al. (1994) reported a clinical trial comparing the use of a spacer combined with a Finish generic BDP inhaler and with the proprietary MDI. No differences in efficacy were seen. Two generic beclomethasone dipropionate (BDP) inhalers, which are commercially available in the UK, were compared in conjunction with the Volumatic spacer, with Becloforte (Kenyon et al., 1995). The generic products were found to give lower respirable doses than the proprietary one, although there was a high degree of variation in the results between replicate experiments. Also, the relative amounts of the fractions in the potentially respirable range were different to those expected (Barnes and Nash, 1996).

The Volumatic spacer is marketed specifically for use with Becloforte, and products from the same manufacturer (Volumatic patient information leaflet), but is used in clinical practice with other products. In view of the questions raised by previous work, we used an aerodynamic particle sizing method to study the amount of BDP available for respiration from four different 250 μg per dose MDI products, used in combination with the Volumatic spacer. The effect of increased residence time within the spacer was also studied, simulating the actual technique which may be used by some patients.

2. Methods and materials

2.1. Materials

The beclomethasone dipropionate 250 μg per dose inhalers were Becloforte (obtained from within the UK, Allen and Hanburys, Uxbridge, Middlesex), Becloforte (imported from Spain by Dowelhurst, Warwick, UK), Beclazone 250 (Norton Healthcare, Harlow, UK) and Filair Forte (3M Health Care, Loughborough, UK). One batch of each product was tested, although some additional testing was done with a second batch of Filair Forte. Five inhalers were tested from each batch. The spacer was a Volumatic (Allen and

Hanburys, Uxbridge, Middlesex). The contact switch and timer were made by the Medical Engineering Department, City Hospital, Birmingham.

The BDP for use as an analytical standard was a gift from Norton Healthcare. The filter used in stage 4 of the impinger was type GF/A (Whatman International, Maidstone, UK). All other chemicals were of analytical or HPLC grade.

2.2. Methods

A multi-stage liquid impinger (Copley Instruments, Nottingham, UK), was used for the determination of aerodynamic particle size distribution. The impinger was operated at 60 l/min, measured without the MDI placed in its throat. Methanol (20 ml) was used in each of the impingement chambers (stages 1–3) and a GF/A filter was used in the final stage.

Five inhalers were tested from each batch studied. A unit from each batch was tested in sequential order to minimise the effect of any day to day bias. With the second batch of Filair Forte, all the units were tested consecutively after the conclusion of testing the other products.

The mouthpiece of the Volumatic spacer was inserted to a depth of 13 mm into the multi-stage liquid impinger throat and was held in a jig to ensure correct alignment. The gap between the mouthpiece and throat was sealed with adhesive putty (Blutack). The spacer was covered with damp paper tissue to reduce the possibility of adverse effects due to electrostatic charge. A contact switch was attached to the top of the canister of the inhaler to be tested. The inhaler was shaken for 30 s and two actuations discarded to waste. It was then inserted in the Volumatic. Actuation of the inhaler into the Volumatic operated the contact switch, starting the multi-stage liquid impinger vacuum pump running for 5 s, to draw the dose through. A total of ten actuations per inhaler were made into the Volumatic, with a minimum 5 s delay between actuations, during which the inhaler was gently agitated. The stages of the multi-stage liquid impinger, the actuator and valve stem of the inhaler and the Volumatic spacer were extracted with methanol to recover the BDP and analysis was performed by HPLC with UV detection as previously described (Barnes and Nash, 1996).

A further series of tests were also performed with the contact switch operating an electronic timer to give a 3.0 s delay between actuation of the inhaler and switching the pump on, to provide a reproducible aerosol residence time within the spacer.

The effect on particle size determination of the acceleration phase, following starting the vacuum pump was studied using two inhalers from each source ($n = 8$), by activation into the Volumatic with the pump already running. The results were analysed by the Signed Ranks test.

Statistical comparison of the products was by one way ANOVA, with pair-wise comparison by t-test where appropriate. The effect of residence time on each product was studied using paired t-tests. The critical value of significance was set at $P = 0.05$ (two tailed) in each case.

3. Results and discussion

The particle size distribution of drug emitted from an MDI may be determined by inertial impingement techniques, such as the multi-stage liquid impinger (Aiache et al., 1993). This enables particles to be determined in four aerodynamic particle size fractions of >13, 13–6.8, 6.8–3.1 and <3.1 μm. Stages 3 and 4 of the multi-stage liquid impinger (<6.8 μm), collect the potentially respirable fraction. Coarse material (greater than approximately 25 μm) is collected at a right-angled connection between the inhaler and multi-stage liquid impinger (known as the throat).

The mean day to day recovery of 1680 μg BDP spiked into the Volumatic spacer ($n = 4$) was 107.2% (range 105.7–111.1%). The recovery and precision of BDP analysis from the other components has been reported previously (Barnes and Nash, 1996), and was in the range 99–109% of the theoretical amounts.

During testing, the temperature was in the range 20–22°C and the relative humidity was in the range 41–51%.

In clinical use, there may be a delay between actuation of the MDI into the spacer and inhal-

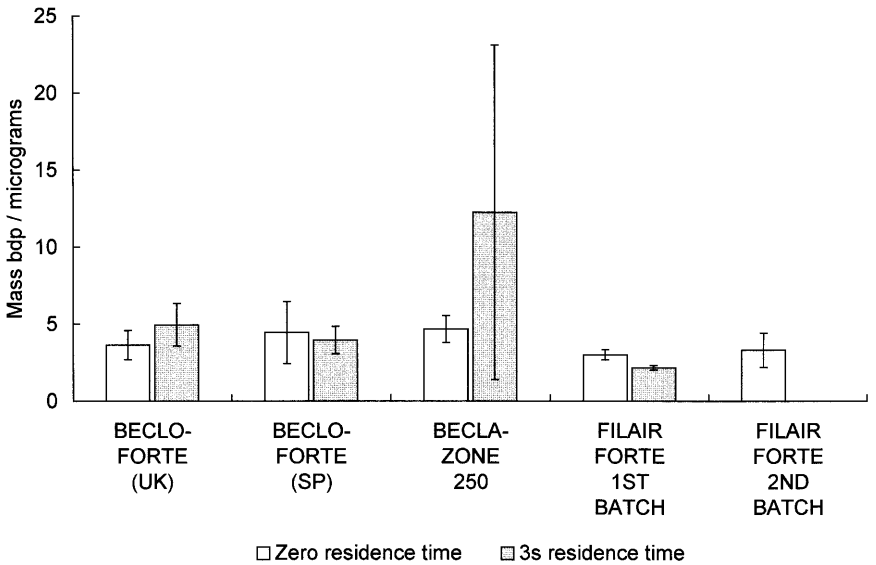

Fig. 1. Deposition of BDP on the throat section (± S.D.).

ing. For instance, in cases where patients experience difficulty in actuating the inhaler with the spacer mouthpiece in the mouth, the Volumatic patient instruction leaflet permits the patient to release the dose from the inhaler before placing the spacer mouthpiece in the mouth. A 3 s delay between actuation of the inhaler and operation of the impinger vacuum pump was therefore studied to simulate possible patient use. In order to avoid inaccuracies in timing and technique due to manually operating the equipment, an electronic timer was used which switched on the pump after 3.0 s. There would therefore be a period during which the pump was accelerating and the air was moving slower than at equilibrium. This could lead to bias in the determination of aerodynamic particle size, since testing is normally by actuation of the inhaler into the multi-stage liquid impinger with the pump already running. This modification to the testing technique was validated by comparing results from eight units, selected from all product sources, tested by actuation through the Volumatic with either the multi-stage liquid impinger pump already running, or started automatically on actuation of the inhaler (zero residence time). There were no significant differences among either the < 3.1 or < 6.8 μm fractions, indicating that the test method would not have a significant effect on the determination of drug in the potentially respirable size range. However, the results for the throat section of the multi-stage liquid impinger, which simulates oropharyngeal drug deposition, were significantly higher with the automatic pump start. The results for this fraction were an average of 30% (1.1 μg) higher than for testing by actuation with the pump already running. The reason for this was not investigated, but this relatively small mass would not affect interpretation of the results.

The Spanish version of Becloforte, which is licensed for use in the UK as a parallel imported product, had an actuator which was visually similar, but not identical to that of the UK version. It was therefore tested to provide a comparison with the UK product.

The mean total mass of BDP emitted for each batch was calculated by summation of the masses collected on each individual component. In all but two cases, this was $\pm 3\%$ of the value obtained from testing the same units without the Volumatic (Barnes and Nash, 1996). The exceptions were recoveries of 92% for Spanish Becloforte and a further result of 92% for Filair Forte (first batch), both tested with a 3 s residence time.

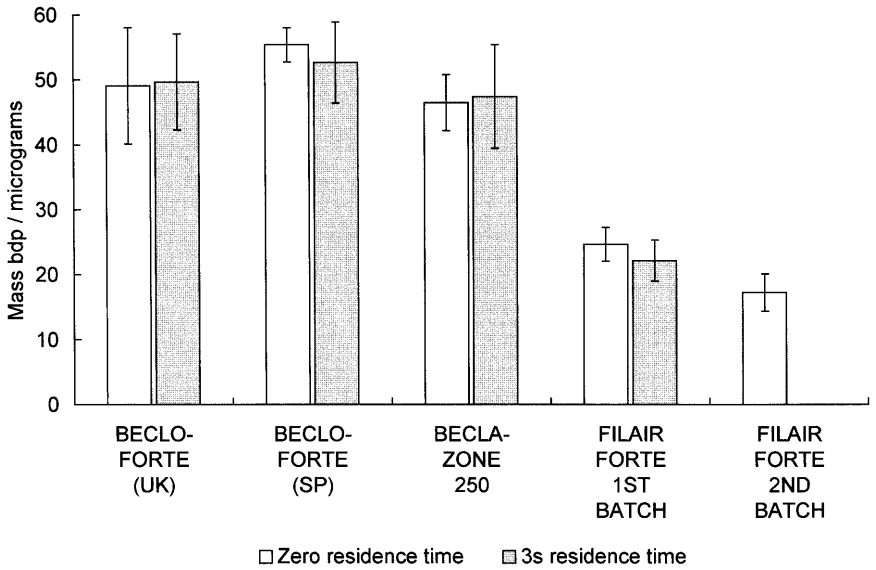

Fig. 2. Deposition of BDP in the <6.8 μm combined fractions ($\pm$S.D.).

Deposition in the impinger throat (Fig. 1) was compared to previously published data without the spacer (Barnes and Nash, 1996). With zero residence time, analysis of variance showed no significant differences among products. With the 3 s residence time, there was a significant difference. Pair-wise t-tests showed significant differences between Filair Forte and Spanish-origin Becloforte and between Filair Forte and UK-origin Becloforte. However, the magnitude of these differences were low (Fig. 1). The relatively high mean and high S.D. seen with Beclazone 250 was due to the result for a single unit of 31.4 μg. The other four units of this product gave values in the range 4.8–9.7 μg. Overall, there were no substantial differences in deposition at the impinger throat, however direct correlation with oropharyngeal drug deposition in the clinical situation is not possible.

The fractions of drug with aerodynamic particle size <6.8 μm are in the potentially respirable range. However, particles of size towards the higher end of this range have relatively low probability of penetrating to peripheral areas of the lung (Hickey, 1992). It has been suggested that the relative proportions of BDP in the size ranges <6.8 and <3.1 μm is of importance (Kenyon et al., 1995). Deposition of BDP in both of these size ranges was therefore studied (Figs. 2 and 3).

Filair Forte (first batch studied) gave significantly less deposition at both <6.8 and <3.1 μm than the other products when tested with either zero residence time or a 3 s residence time. This is despite having a good physical fit in the Volumatic. Compared to Becloforte (UK origin), with zero residence time, there was 49.8% less in the 6.8 μm fraction and 58.4% less in the <3.1 μm fraction. With a 3 s residence time, the corresponding reductions were 55.4 and 69.6% respectively. A second batch of Filair Forte gave similar results to the first (Figs. 2 and 3), but was not included in the statistical analysis because it was tested in isolation, after completion of the main study.

Since inhaled BDP has an approximately linear dose-response relationship (Toogood et al., 1977), the use of Filair Forte through the Volumatic would be expected to result in poorer clinical effect for an equivalent dosage than the other products.

All the products studied had a good physical fit in the Volumatic. The reason for the lower delivery of potentially respirable dose from Filair Forte is presumably due to the characteristics of

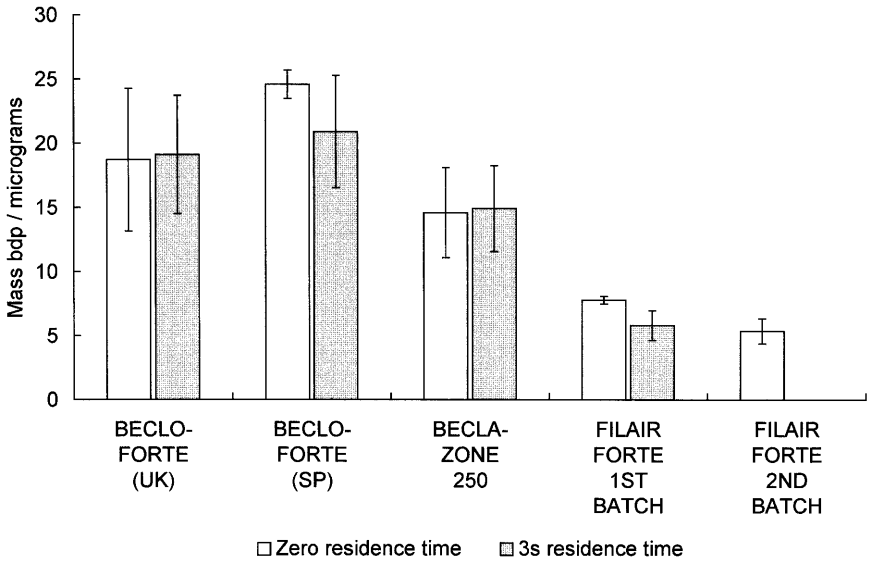

Fig. 3. Deposition of BDP in the < 3.1 μm fraction ($\pm$ S.D.).

the aerosol plume emitted. When used without the Volumatic, this product has a similar output in the < 6.8 μm fraction to the other products (Kenyon et al., 1995; Barnes and Nash, 1996).

At < 6.8 μm, the only other significant difference was between Becloforte (Spanish) and Beclazone 250, when tested with zero residence time. At < 3.1 μm with zero residence time, Becloforte (Spanish) had significantly higher deposition than all the other products, including the UK version of Becloforte. With 3 s residence time, deposition < 3.1 μm was significantly greater with Becloforte (Spanish) than Beclazone 250. The magnitude of these differences were, however, less marked than those with Filair Forte (Figs. 2 and 3).

The experiments were not discriminating enough to detect any relatively small differences between products. The 95% confidence limits for the difference between < 6.8 μm means, for the comparison of Becloforte (UK) with Beclazone 250, with zero residence time, was $-4.5 - +9.7$ μg per actuation. With 3 s residence time, the 95% confidence limits were $-6.4 - +10.9$ μg.

The relative order of BDP deposition in the range < 3.1 μm was in the order Becloforte > Beclazone 250 > Filair Forte. This is in agreement with the data of Kenyon et al. (1995). However, these authors found a similar marked trend in the results in the < 6.8 μm range, whereas in the present study, little difference was found between Becloforte and Beclazone 250.

The residence time within the spacer had no significant effect on deposition in the < 6.8 or < 3.1 μm fractions with Becloforte (UK or Spanish) or Beclazone 250. This suggests that sub-optimal patient co-ordination would not be expected to have a detrimental effect on the performance of these products. With Filair Forte, there was significantly less at < 3.1 μm, but not at < 6.8 μm. It is not therefore possible to predict any possible changes due to sub-optimal inhalation technique with this product.

O'Callaghan et al. (1994) studied the effect of varying the residence time upon the aerodynamic particle size distribution, using Becloforte and Becotide inhalers with the Volumatic spacer. A residence time of 5 s made little difference to the deposition in the potentially respirable size range, compared to a 1 s time. This is in agreement with the present work. However, these authors found that the amount of the potentially respirable fraction was not decreased, compared to testing the inhalers without a spacer. In the present study, there was a reduction in the < 6.8 μm fraction,

compared to testing the same batch of MDI without the spacer (Barnes and Nash, 1996) of 42.9% for Becloforte (UK), 43.7% for Becloforte (Spanish), 43.4% for Beclazone 250 and 69.5% for Filair Forte. The magnitude of the reduction was similar in the < 3.1 μm range. This reduction occurred despite the steps taken to minimise the effects of electrostatic charge. The dimensions of the inertial impactor sampling inlet (Fults et al., 1991) or the depth of insertion of the actuator, with some formulations of MDI, into a simulated oropharynx (Miller and Purrington, 1996) affected the amount of potentially respirable drug. It is therefore possible that the reason for the observed reduction is due to the method of connecting the Volumatic to the multi-stage liquid impinger inlet. This could be caused, for instance, by differences in turbulence experienced within the throat section of the multi-stage liquid impinger. However, the results nevertheless indicate the differences and similarities between the products involved.

4. Conclusion

Compared to the other combinations, the use of the Volumatic with Filair Forte would be expected to result in poorer delivery of drug to the lung periphery.

No substantial differences in performance could be detected between Spanish-origin Becloforte, UK-origin Becloforte or Beclazone 250, even when tested with a moderately extended residence time within the Volumatic spacer.

Further work would be required to determine the practical significance of the differences in the < 3.1 μm fraction, or of the performance of the other available strengths of beclomethasone dipropionate MDI which are available.

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